Clinical Efficacy and Safety Analysis on Targeted Nursing Intervention Combined with Drug Therapy of Aspirin and Clopidogrel in the Treatment of Ischemic Stroke

Wanjiao Tang
Chilei Ma

Objective. The purpose of the study was to investigate the clinical efficacy and safety of targeted nursing intervention combined with drug therapy of aspirin and clopidogrel in the treatment of ischemic stroke. Methods. A total of 118 ischemic stroke patients admitted to our hospital from January 2018 to January 2020 were selected and divided into control group (n=59) and experimental group (n=59) according to the order of admission, and their clinical data were retrospectively analyzed. Among them, the control group patients were treated with aspirin, while the patients in the experimental group received the drug therapy of aspirin combined with clopidogrel. After that, the indexes related to the clinical efficacy and safety of treatment were compared between the two groups. Results. The total effective rate of treatment in the experimental group was significantly higher than that in the control group; the NIHSS and ADL scores in both groups after treatment were significantly better than those before treatment, and after treatment, the NIHSS and ADL scores in the experimental group were significantly better than those in the control group; the serum hs-CRP levels and platelet aggregation rate of the patients after treatment were significantly lower than those before treatment, and the serum hs-CRP levels and platelet aggregation rate of the patients in the experimental group were lower than those in the control group, and after treatment, the mean hs-CRP levels of the patients in the experimental group were within the normal range, with statistically significant differences; during treatment, there were 2 cases of epistaxis in the control group, and 1 case of epistaxis as well as 2 cases of gingival bleeding in the experimental group, and there were no adverse reactions occurring in patients' skin and mucosa, digestive tract, brain, etc. Conclusion. Over a short period of time, targeted nursing intervention combined with drug therapy of aspirin and clopidogrel, with obvious clinical efficacy and high safety, can effectively improve serum hs-CRP levels, inhibit platelet aggregation as well as improve prognosis in patients.

Keywords: ischemic stroke; safety; clopidogrel; aspirin; targeted nursing
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Ischemic stroke, also known as cerebral infarction, refers to a blood supply disorder caused by a variety of cerebral vascular diseases, whose main manifestation is anoxic and ischemic necrosis, and after onset, patients' neurological function will be greatly damaged. Clinical statistics have shown that the incidence of ischemic stroke accounts for 70-80% of that in cerebrovascular diseases [1-4]. Due to the impaired neurological function in patients, they may suffer from aphasia, hemiplegia, ataxia, sensory disturbance and other symptoms; therefore, the nursing care for the ischemic stroke patients must be performed by making a detailed and targeted nursing plan according to their own conditions, so as to achieve better therapeutic effect of nursing intervention [5-8]. Generally, the pathogenesis and triggers of ischemic stroke are relatively complex, such as hypertension, hypeluricemia, thrombocytosis, unbalanced diet, or alcohol abuse, and the coexistence of many factors

Wanjiao Tang Department of International Special Needs Medical, Shengli Oilfield Central Hospital, Dongying, 257034, Shandong Province, China, Chilei Ma Department of Chinese medicine, Shengli Oilfield Central Hospital, Dongying, 257000, Shandong Province, China*
**Corresponding author: Department of Chinese medicine, Shengli Oilfield Central Hospital, NO.31, Jinan Road, Dongying, 257034, Shandong Province, China (E-mail: shaihao3429803187@163.com)*

may also contribute to the local insufficient blood supply in patients' brain tissue. Platelets play an important role in atherosclerosis, and thus, the inhibition of platelet activity is of great significance to relieve patients' symptoms of ischemic stroke and improve their neurological function, and meanwhile, the platelet inhibitors, aspirin and clopidogrel, have gained great popularity in clinical treatment. Based on this, this paper investigated the therapeutic effect and safety of aspirin combined with clopidogrel in the treatment of ischemic stroke under the premise of targeted nursing intervention, and the study results are summarized as follows.

MATERIALS AND METHODS

General Information

A total of 118 ischemic stroke patients admitted to our hospital from January 2018 to January 2020 were selected and divided into control group (n=59) and experimental group (n=59) according to the order of admission, and their clinical data were retrospectively analyzed. In the control group, there were 6 patients with hypertension and arrhythmia, 19 patients with hypertension and diabetes and 34 patients with hypertension alone, with the male to female ratio of 33:26, age of (67.3 ± 4.5) years old and disease course of (17.3 ± 2.1) d. In the experimental group, there were 8 patients with hypertension and arrhythmia, 18 patients with hypertension and diabetes and 33 patients with hypertension alone, with the male to female ratio of 32:27, age of (68.7 ± 4.6) years old and disease course of (17.1 ± 2.4) d. There were no statistically significant differences in the general information of the patients between the two groups, with research significance (P > 0.05).

Table 1
Comparison of the general information of the patients between the two groups

	Control group (n=59)	Experimental group (n=59)	t/X^2	P
Age (years old)	(67.3±4.5)	(68.7±4.6)	1.6711	0.0974
Disease course (d)	(17.3±2.1)	(17.1±2.4)	0.4817	0.6309
BMI (kg/m^2)	(17.6±2.2)	(17.4±2.1)	0.5051	0.6144
Smoking			0.1388	0.709
Yes	24 (40.68)	26 (44.07)		
No	35 (59.32)	33 (55.93)		
Drinking			1.2494	0.264
Yes	31 (52.54)	37 (62.71)		
No	28 (47.46)	22 (37.29)		
Gender			0.0343	0.853
Male	33 (55.93)	32 (54.24)		
Female	26 (44.07)	27 (45.76)		
Place of residence			0.3065	0.580
Urban area	26 (44.07)	29 (49.15)		
Rural area	33 (55.93)	30 (50.85)		

Inclusion Criteria

① Patients met the clinical diagnostic criteria for ischemic stroke in the *Key Diagnostic Points for Cerebrovascular Diseases*, and they were confirmed by MRI examination or head CT. ② Patients were those who underwent first onset. ③ Patients had their largest lesion diameter of less than or equal to 1.5 cm. ④ This study was approved by the Hospital Ethics Committee, and patients and their family members were informed of the purpose and process of the study and signed the informed consent.

Exclusion Criteria

① Patients had cerebral hemorrhage, severe cardiovascular diseases or hepatic and renal diseases. ② Patients received the treatment with thrombolytics or anticoagulants within nearly one month. ③ Patients had disease onset longer than 48 hours, and they were allergic to the drugs used in this study. ④ Patients had cognitive disorders, or refused to cooperate with others.

Methods

All patients were given 10 mg of atorvastatin every night for intensive lipid lowering, and meanwhile symptomatic treatment for reducing blood pressure, protecting brain cells, improving cerebral microcirculation and lowering glucose sugar was carried out. Based on that, the patients also received antiplatelet therapy for one month.

In the control group, the patients took aspirin enteric-coated tablets (Specification: 100mg*30 tablets; Manufacturer: Bayer Healthcare Co., Ltd.; State Food and Drug Administration approval number: J20130078) orally before meals, with the first dose of 300 mg and 100-200 mg/d thereafter.

In the experimental group, the patients took aspirin enteric-coated tablets combined with clopidogrel hydrogen sulphate tablets (Specification: 75mg; Manufacturer: Hangzhou Sanofi Pharmaceutical Co., Ltd.; State Food and Drug Administration approval number: J20180029) orally once daily, with 75 mg a time. The medication cycle of the patients in both groups was 30 days.

All patients received targeted nursing intervention, and specific steps were as follows. ① Ward environment management. The wards were ventilated with fresh air twice a day to ensure good ventilation and air circulation, and were disinfected once daily to ensure clean and tidy environment, with keeping the room temperature at 18-20 °C and the humidity of 50-60 % [9-10]. ② Psychological intervention and health education. Medical staff should actively communicate with patients, pay attention to their emotional changes and carry out regular assessment of their psychological states, so as to timely eliminate their fear, irritability, restlessness and anxiety. In addition, medical staff should actively communicate with patients' family members to obtain cooperation and support from them; especially, before treatment, medical staff should explain the pathogenesis and progress of the disease, risk factors and nursing notice to both patients and their family members, timely answer their questions, popularize the health knowledge related to ischemic stroke, provide more confidence for them through introducing some successful cases, as well as help them relax their body and mind through playing soothing music [11-12]. ③ Diet nursing. According to the dietary nutrition guidelines and principles of high protein, low fat, high fiber, bland and light diets, reasonable diets properly combined with patients' taste preferences should be made. Besides, salty, spicy and greasy foods should be also be controlled or even inhibited. ④ Rehabilitation training. At the very beginning, patients should perform limb training mainly including external rotation, internal rotation, flexion-extension, abduction and others for 30 minutes daily, and when their conditions remained stable, they should be instructed to carry out rehabilitation training such as standing, walking and climbing stairs. After a period of time, the patients should carry out further training of grasping, page turning, etc., and meanwhile they should conduct sound-making training. All these kinds of training should be performed from being simple to being difficult. ⑤ Posture nursing. The bed tail should be elevated approximately 15-30 ° C to keep patients in low-head and high-foot positions, and their postures should be changed once every 2-3 hours. Additionally, medical staff should give patients proper massage 3-5 times a day to promote blood circulation.

Observation Indexes

Clinical efficacy. The markedly effective referred to that compared with that before treatment, the NIHSS score reduced more than 90% after treatment, the ADL score was more than 90 points, patients' muscle strength was grade IV-V, all imaging results and examination indexes basically restored to normal levels, there was no focal neurological dysfunction and patients recovered consciousness; the effective referred to that compared with that before treatment, the NIHSS score reduced 40-89% after treatment, and the ADL score was 40-90 points, patients basically recovered consciousness, patients' vital signs basically restored to normal levels and there was mild neurological dysfunction; the ineffective referred to that patients' clinical conditions had no significant improvement or even aggravated. Effective rate of treatment = (markedly effective + effective) / total number × 100%.

NIHSS and ADL scores. The physical function of the patients between the two groups before and after treatment was evaluated by the *National Institutes of Health Stroke Scale* (NIHSS) and the *Barthel Indexes of Activity of Daily Living Scale* (ADL), In the NIHSS, higher scores indicated more severely impaired neurological function, with the total score of 42 points, while in the ADL, with the total score of 100 points, higher scores indicated better self-care ability in daily life. The evaluation should be performed by an experienced neurological physician.

Serum hs-CRP detection. After fasting venous blood samples were taken from the patients, serum was taken after centrifugation, and hs-CRP levels were measured by the latex enhanced immunoturbidimetric assay, with the detection range of 0.1-320 mg/L and the normal range of 0.1-5 mg/L.

Platelet aggregation rate. Platelet granule membrane protein 140 (GMP-140) levels were measured in patients, and platelet aggregation rate was determined after arachidonic acid and

adenosine diphosphate were taken as inducers.

Safety. The patients in both groups received head CT, liver and kidney function examinations as well as blood routine examination, so as to check whether they had hemorrhage in brain, skin and mucosa, digestive tract, etc. or severe allergy during medication.

Statistical Treatment

The selected data processing software for this study was SPSS20.0, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to draw the pictures of the data. Measurement data were tested by t-test and enumeration data were tested by X^2 test and normality test. The differences had statistical significance when $P < 0.05$.

RESULTS

Comparison of Clinical Efficacy between Two Groups

The effective rate of treatment in the experimental group was significantly higher than that in the control group ($P < 0.05$), with statistically significant differences, as shown in Table 2.

Table 2
Comparison of clinical efficacy between two groups [n (%)]

Group	Ineffective	Effective	Markedly effective	Total effective rate
Control group (n=59)	15 (25.42)	25 (42.37)	19 (32.21)	44 (74.58)
Experimental group (n=59)	6 (10.17)	23 (38.98)	30 (50.85)	53 (89.83)
X^2				4.6922
P				0.030

Comparison of Nihss and Adl Scores between the Two Groups

The NIHSS and ADL scores after treatment in both groups were significantly better than those before treatment, and after treatment, the NIHSS and ADL scores in the experimental group were significantly better than those in the control group (all $P < 0.05$), with statistically significant differences, as shown in Table 3.

Table 3
Comparison of NIHSS and ADL scores before and after treatment between the two groups ($\bar{x}\pm s$)

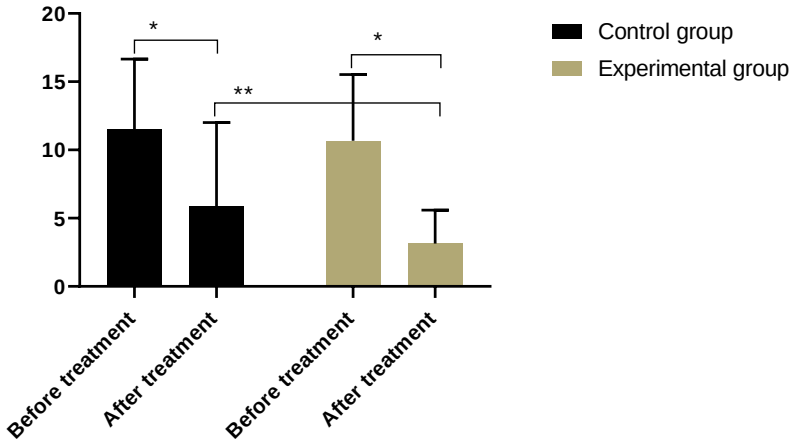
Group	NIHSS score		ADL score	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=59)	21.39±2.46	16.72±2.25*	30.22±5.27	41.30±6.81*
Experimental group (n=59)	21.45±2.53	11.44±1.73*	30.31±5.32	53.41±8.22*
t		14.2895		8.7141
P		0.000		0.000

* indicated the comparison with the scores before treatment, $P < 0.05$.

Comparison of Serum Hs-Crp Levels between the Two Groups

The serum hs-CRP levels of the patients after treatment were significantly lower than those before treatment; after treatment, the serum hs-CRP levels of the patients in the experimental group were lower than those in the control group, and the mean hs-CRP levels in the experimental group were within the normal range, with statistically significant differences, as detailed in Figure 1.

Figure 1
Comparison of serum hs-CRP levels between the two groups ($\bar{x}$±s)



Note: The abscissa represented before and after treatment, while the ordinate represented serum hs-CRP level, mg / L.

In the control group, the serum hs-CRP levels before and after treatment were (11.52 ± 5.14) and (5.89 ± 6.12), respectively.

In the experimental group, the serum hs-CRP levels before and after treatment were (10.67 ± 4.85) and (3.14 ± 2.45), respectively.

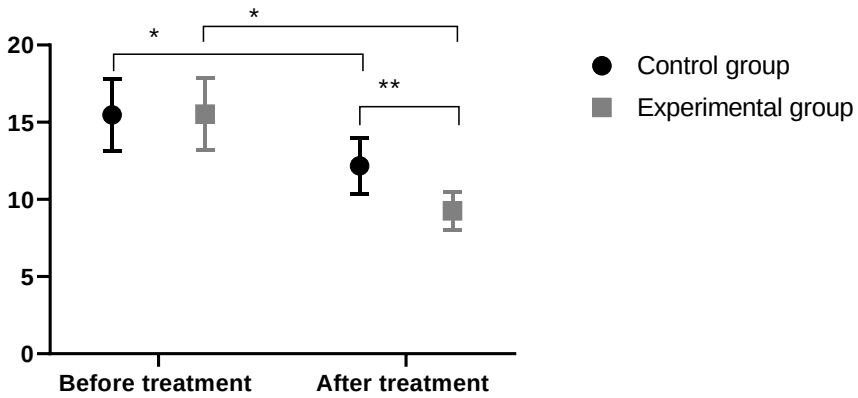
* from left to right indicated that there were significant differences in hs-CRP levels before and after treatment in the control group and experimental group, respectively (t = 4.2000, 10.6445, P = 0.0001, 0.000).

** indicated that there were significant differences in serum hs-CRP levels between the two groups after treatment (t = 3.2043, P = 0.0017).

Comparison of Platelet Aggregation Rate between the Two Groups

The indexes of platelet aggregation rate after treatment in both groups were lower than those before treatment, and the indexes of platelet aggregation rate in the experimental group were significantly lower than those in the control group, with statistically significant differences, as shown in Figure 2, 3 and 4.

Figure 2
Comparison of GMP-140 levels between the two groups ($\bar{x}$±s)



Note: The abscissa represented before and after treatment, while the ordinate represented GMP-140 level, μg/L.

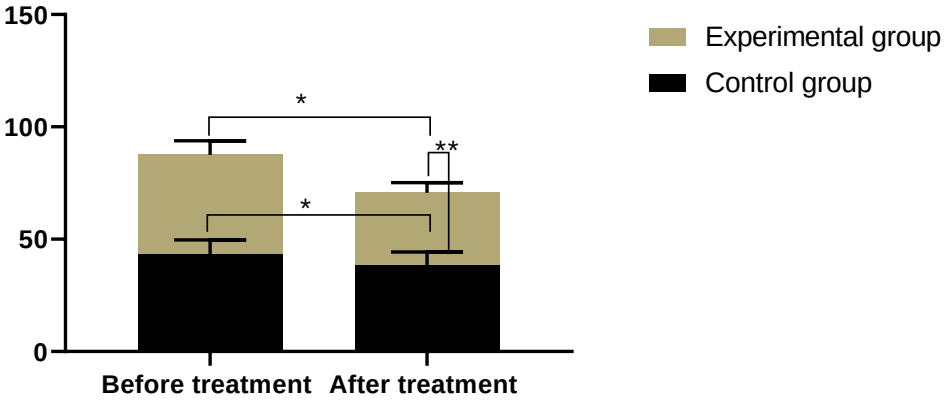
In the control group, the GMP-140 levels before and after treatment were (15.47 ± 2.31) and (12.18 ± 1.82), respectively.

In the experimental group, the GMP-140 levels before and after treatment were (15.53 ± 2.34) and (9.25 ± 1.24), respectively.

* from bottom to top indicated that there were significant differences in GMP-140 levels before and after treatment in the control group and experimental group, respectively (t = 8.5931, 18.2149, all P < 0.001).

** indicated that there were significant differences in GMP-140 levels between the two groups after treatment (t = 10.2193, P = 0.000).

Figure 3
Comparison of platelet aggregation rate induced by ADP between the two groups ($\bar{x}$±s)



Note: The abscissa represented before and after treatment, while the ordinate represented platelet aggregation rate, %.

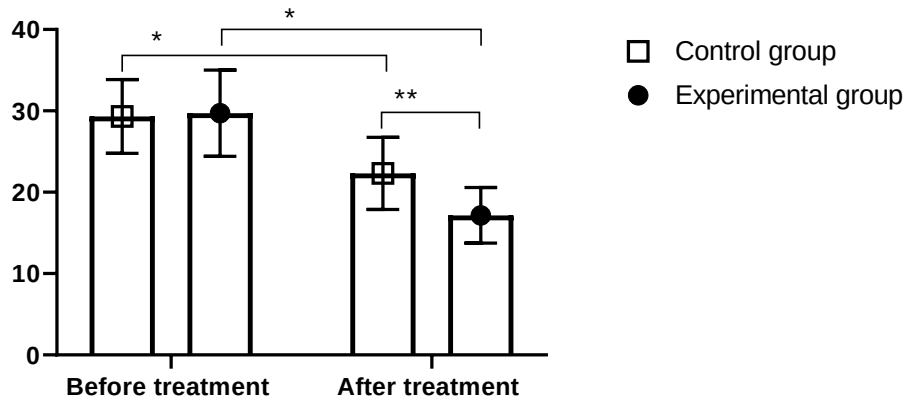
In the control group, the platelet aggregation rate induced by ADP before and after treatment were (43.46 ± 6.17) and (38.62 ± 5.66), respectively.

In the experimental group, the platelet aggregation rate induced by ADP before and after treatment were (44.07 ± 6.28) and (32.11 ± 4.47), respectively.

* from bottom to top indicated that there were significant differences in platelet aggregation rate induced by ADP before and after treatment in the control group and experimental group, respectively (t = 4.4402, 11.9177, respectively, all P < 0.001).

** indicated that there were significant differences in platelet aggregation rate induced by ADP between the two groups after treatment (t = 6.9332, P = 0.000).

Figure 4
Comparison of platelet aggregation rate induced by AA between the two groups ($\bar{x}$±s)



Note: The abscissa represented before and after treatment, while the ordinate represented platelet aggregation rate, %.

In the control group, the platelet aggregation rate induced by AA before and after treatment were (29.32 ± 4.54) and (22.31 ± 4.43), respectively.

In the experimental group, the platelet aggregation rate induced by AA before and after treatment were (29.71 ± 5.31) and (17.16 ± 3.41), respectively.

* from bottom to top indicated that there were significant differences in platelet aggregation rate induced by AA before and after treatment in the control group and experimental group, respectively (t = 8.4886, 15.2755, all P < 0.001).

** indicated that there were significant differences in platelet aggregation rate induced by AA between the two groups after treatment (t = 7.0760, P = 0.000).

Comparison of Medication Safety between the Two Groups

During treatment, there were 2 cases of epistaxis in the control group, and 1 case of epistaxis as well as 2 cases of gingival bleeding in the experimental group, and there were no adverse reactions occurring in skin and mucosa, digestive tract, brain, etc.

DISCUSSION

Based on the fact that occurrence of stroke is largely related to platelet activation, the greatly activated platelet can increase platelet aggregation rate, which further leads to cerebral infarction. In addition to the treatment measures of blood pressure lowering and symptomatic treatment, the inhibition of platelet aggregation is also a very critical therapeutic step in clinical treatment of ischemic stroke. Clopidogrel and aspirin, two effective anti-platelet agents, are commonly used to prevent cardiovascular diseases in clinical practise [13-16]. Aspirin can inhibit the activity of platelet cyclooxygenase (COX) to acetylate serine residues of COX, thereby irreversibly inhibiting COX-1; at the same time, it can also block the metabolic pathway of arachidonic acid that cannot synthesize prostaglandin (TXA_2), which leads to the failure of synthesis of thromboxane A_2, thus reducing platelet TXA_2 levels, inhibiting platelet aggregation and weakening platelet activity. Plus, the inhibition of platelets by aspirin can sustain the whole life cycle of platelets, so it is of great importance in the prevention and treatment of cerebrovascular diseases. Clinical studies have shown that aspirin can inhibit 95% of platelets in patients, and the remaining inhibition may be related to collagen, epinephrine and adenosine diphosphate [17-20]. Clopidogrel can exert irreversibly inhibitory and blocking effect on the processes of platelet P2Y12 receptor binding to adenosine diphosphate, which can disrupt platelet membrane glycoprotein receptor complexes, block intracellular signaling pathways and inhibit platelets from releasing more adenosine diphosphate, thereby preventing platelet aggregation. Although aspirin can inhibit COX, it has no effect on adenosine diphosphate, so that drug alone does not serve the function of complete inhibition, and long-term administration can trigger various gastrointestinal diseases or even the formation of drug resistance. However, aspirin not only does not inhibit the antiplatelet effect of clopidogrel, but also elevates the platelet blocking effect of aspirin, so the combination of these two drugs together can greatly reduce drug resistance [21-24].

In this study, the results revealed that the total effective rate of treatment in the experimental group was significantly higher than that in the control group; the NIHSS and ADL scores in both groups after treatment were significantly better than those before treatment, and after treatment, the NIHSS and ADL scores in the experimental group were significantly better than those in the control group; the serum hs-CRP levels and platelet aggregation rate of the patients after treatment were significantly lower than those before treatment, and the serum hs-CRP levels and platelet aggregation rate of the patients in the experimental group were lower than those in the control group, and after treatment, the mean hs-CRP levels of the patients in the experimental group were within the normal range, with statistically significant differences; during treatment, there were 2 cases of epistaxis in the control group, and 1 case of epistaxis as well as 2 cases of gingival bleeding in the experimental group, and there were no adverse reactions occurring in skin and mucosa, digestive tract, brain, etc. Therefore, over a short period of time, targeted nursing intervention combined with drug therapy of aspirin and clopidogrel, with obvious clinical efficacy and high safety, can effectively improve serum hs-CRP level, inhibit platelet aggregation and improve prognosis in patients. Our study results are consistent with the findings of Annie Pedersen [25] and others, who have pointed out in their studies that the combination of aspirin and clopidogrel can better improve the neurological impairment of stroke patients and greatly inhibit platelets, with high safety and no adverse reactions occurring in patients.

In conclusion, the mechanism of aspirin combined with clopidogrel has some complexity, which may be related to the downstream process of fighting against platelet aggregation of the drugs. Additionally, the targeted nursing intervention combined with drug therapy of aspirin and clopidogrel is better than medication alone for the treatment of ischemic stroke, with high safety. However, there are also some limitations in this study, such as small number of samples and single-center researches. Therefore, more reliable studies should be conducted by expanding study samples and promoting multi-center researches.

REFERENCES

1. **Fierus M.A randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic effects of a targeted exposure of intravenous repinotan in patients with acute ischemic stroke: modified Randomized Exposure Controlled Trial**

(mRECT).[J].Stroke: A Journal of Cerebral Circulation,2009,40(11):3518-3525.
2. Cheryl B. Lin,Eric D. Peterson,Eric E. Smith, et al.Emergency Medical Service Hospital Prenotification Is Associated With Improved Evaluation and Treatment of Acute Ischemic Stroke[J].Circulation. Cardiovascular quality and outcomes.,2012,5(4):514-522.
3. Gutierrez, Jose,Hatleberg, Camilla Ingrid,Evans, Henry, et al.Role of pre-stroke immunity in ischemic stroke mechanism among patients with HIV[J].AIDS care.,2019,31(2):270-274.
4. Hills Nancy ,Johnston S Claiborne.Duration of hospital participation in a nationwide stroke registry is associated with improved quality of care[J].,2006,(1):20.
5. Mitchell, Peter J.,Yan, Bernard,Brozman, Miroslav, et al.Plasmin (Human) Administration in Acute Middle Cerebral Artery Ischemic Stroke: Phase 1/2a, Open-Label, Dose-Escalation, Safety Study[J].Journal of stroke and cerebrovascular diseases: The official journal of National Stroke Association,2017,26(2):308-320.
6. Furtado C,Silver L,Harrison P, et al.Screening for aspirin responsiveness after transient ischemic attack and stroke: comparison of 2 point-of-care platelet function tests with optical aggregometry.[J].Stroke: A Journal of Cerebral Circulation,2005,36(5):1001-1005.
7. Kirkman, Matthew A.,Lambden, Simon,Smith, Martin.Challenges in the Anesthetic and Intensive Care Management of Acute Ischemic Stroke[J].Journal of neurosurgical anesthesiology,2016,28(3):214-232.
8. Nilanont,Y.,Nidhinandana,S.,Suwanwela,N.C., et al.Quality of acute ischemic stroke care in thailand: A prospective multicenter countrywide cohort study[J].Journal of stroke and cerebrovascular diseases: The official journal of National Stroke Association,2014,23(2):213-219.
9. Tanya M. Burton,Tanya M. Burton,Michael Lacey, et al.One-year follow-up healthcare costs of patients hospitalized for transient ischemic attack or ischemic stroke and discharged with aspirin plus extended-release dipyridamole or clopidogrel[J].Journal of Medical Economics,2012,15(6):1217-1225.
10. Zhixin Liu,Rachael Moorin,John Worthington, et al.Using Large - Scale Linkage Data to Evaluate the Effectiveness of a National Educational Program on Antithrombotic Prescribing and Associated Stroke Prevention in Primary Care[J].Journal of the American Heart Association,2016,5(10):n/a-n/a.
11. Lin, Yi,Wang, Anxin,Li, Jiejie, et al.Impact of Glycemic Control on Efficacy of Clopidogrel in Transient Ischemic Attack or Minor Stroke Patients With CYP2C19 Genetic Variants[J].Stroke: A Journal of Cerebral Circulation,2017,48(4):998-1004.
12. ZHOU Yu-ying,LI Pan.Research progress of new antiplatelet drugs in the prevention and treatment for ischemic stroke[J].,2013. DOI:10.3969/j.issn.1672-6731.2013.04.005.
13. Tsai NW,Chang WN,Shaw C.Serial change in platelet activation markers with aspirin and clopidogrel after acute ischemic stroke.[J].Clinical neuropharmacology,2010,33(1):40-45.
14. Meng-chan LIU,Feng-peng LI,Ya-ling HAN, et al.Argatroban versus aspirin plus clopidogrel in the treatment of acute ischemic stroke: a pilot, randomised, open-label study[J].,2015.
15. Nakagami, Hironori,Sasaki, Tsutomu,Morishita, Ryuichi, et al.Therapeutic Vaccine Against S100A9 (S100 Calcium-Binding Protein A9) Inhibits Thrombosis Without Increasing the Risk of Bleeding in Ischemic Stroke in Mice[J].Hypertension: An Official Journal of the American Heart Association,2018,72(6):1355-1364.
16. Balucani C,Cordonnier C,Leys D.Antiplatelet drugs for ischemic stroke prevention.[J].Cerebrovascular diseases,2009,27(Suppl.1):120-125.
17. Genetic polymorphisms and drug interactions leading to clopidogrel resistance: Why the asian population requires special attention[J].International Journal of Neuroscience,2013,123(3):143-154.
18. Zhang, Shihong,Wu, Bo,Liu, Ming, et al.Acupuncture Efficacy on Ischemic Stroke Recovery Multicenter Randomized Controlled Trial in China[J].Stroke: A Journal of Cerebral Circulation,2015,46(5):1301-1306.
19. van der Sluijs, Pieter M.,Jansen, Ivo G. H.,Mulder, Maxim J. H. L., et al.Endovascular Treatment The Role of Dominant Caliber M2 Segment Occlusion in Ischemic Stroke[J].Stroke: A Journal of Cerebral Circulation,2019,50(2):419-427.
20. Mortality and Disability According to Baseline Blood Pressure in Acute Ischemic Stroke Patients Treated by Thrombectomy: A Collaborative Pooled Analysis[J].Journal of the American Heart Association,2017,6(10):n/a-n/a.
21. Smith Shawn M.,Fontaine Gabriel V..Alteplase for Acute Ischemic Stroke after Heparin Reversal with Protamine: A Case Report and Review[J].Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy,2017,37(10):e103-e106.
22. Lee, Yong-Seok,Kim, Eung Gyu,Rha, Joung-Ho, et al.Recurrent Ischemic Lesions After Acute Atherothrombotic Stroke Clopidogrel Plus Aspirin Versus Aspirin Alone[J].Stroke: A Journal of Cerebral Circulation,2016,47(9):2323-2330.
23. Dário Freitas,Ana Alves,Alexandre Pereira, et al.O espessamento da íntima-média associa-se independentemente ao Acidente Vascular Cerebral Isquêmico Increased intima-media thickness is independently associated with Ischemic Stroke[J].,(6):497.
24. Aytekin Akyüz,Ertugrul Bolayir,Sefik Dener, et al.The effect of aspirin, ticlopidine and their low -

dose combination on platelet aggregability in acute ischemic stroke: a short duration follow - up study[J].European Journal of Neurology,1999,6(1):57-61.

25. Annie Pedersen,Tara M. Stanne,Petra Redfors, et al.Fibrinogen concentrations predict long - term cognitive outcome in young ischemic stroke patients[J].Research and Practice in Thrombosis and Haemostasis,2018,2(2):339-346.